IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Spector, Lorraine
Avi ASHKENAZI, *et al.*	)	Art Unit: 1647
Application Serial No. 09/902,615	)	Confirmation No: 9850
Filed: July 10, 2001	)	Attorney's Docket No. 39780-1618 P2C28
For: **ANTIBODIES TO PRO326 POLYPEPTIDES**	)	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On February 4, 2005, the Examiner made a final rejection to pending Claims 39-41 and 43. A Notice of Appeal was filed on August 3, 2005, and Appellants' Appeal Brief was filed on October 3, 2005. A revised Appeal Brief was filed May 15, 2006 and an Examiner's Answer was mailed on August 1, 2006.

The following constitutes the Appellants' Reply Brief in response to the Examiner's Answer and is timely filed. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

I. *Claim Rejection Under 35 U.S.C. §101 and §112, First Paragraph*

Concerning the rejection of Claims 39-41 and 43 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in his Answer, the Examiner cites the following arguments:

(1) "In brief....the assay is *not* by itself, accepted in the art as establishing that it is more likely than not that a compound is a proinflammatory molecule, rather all it establishes is that the molecule is toxic or irritant", (emphasis in original, page 8, lines 14 through 18 of the Examiner's Answer). The Examiner adds that "lye and acid were cited as extreme examples of compositions that would cause the same result observed for PRO326," without providing any evidentiary support from the art for the Examiner's position (page 10, lines 17-18). The Examiner seems to indicate that the SVP (skin vascular permeability assay) is merely an immediate type hypersensitivity assay, and is not indicative of utility for PRO326.

(2) It has *not* been shown *if* **PRO326 is produced *by* the guinea pig**, or under what conditions.

(3) The Examiner finds the SVP results preliminary and asserts that "substantial further experimentation would be required to determine a utility for PRO326." (see pages 11-13; pages 24-25 of Examiner's answer) On pages 23-24, last few lines, the Examiner asserts that "with respect to the use of anti-PRO326 as an anti-inflammatory compound, one would first have to show that PRO326 is *produced* as part of an inflammatory response *in vivo* for such to constitute a substantial assertion. that has not been done." (emphasis in original). The Examiner adds that "the kinetics of the response (has) not been investigated for PRO326. It has *not* been shown that the expression profile of PRO326 is similar to any other protein, as was done by Rampart *et al.*- (reference submitted previously by Appellants with response of July 22, 2003).

Appellants disagree with each of the Examiner's arguments for the reasons detailed below. The Examiner's arguments will be addressed in the order in which they are listed.

Utility Standard

First of all, Appellants respectfully remind the Examiner that an Applicants' assertion of

utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "**unless there is a reason for one skilled in threat to question the objective truth of the statement of utility or its scope.**" (Emphasis added) *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977). Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The Examiner has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." (Emphasis added) *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Appellant to provide rebuttal evidence. *Id.*

Arguments

Appellants assertion of utility is based on the positive reaction in the SVP assay (Example 77 in the instant specification), which is well-known in the art as an assay for identifying inflammatory molecules. This point was discussed in detail in the Declaration by Dr. Sherman Fong, which further sets forth the state of the art in the field of inflammation as a whole, as it existed at the time of the instant filing, and also presents several exemplary references wherein assays similar to the SVP assay were used for identifying candidate inflammatory molecules. Thus, based on the knowledge known and available to one skilled in the art, a positive reaction for PRO326 in the SVP assay would undoubtedly be a showing that PRO326 is an inflammatory

molecule, and further, one skilled in the art would find the Appellants' assertion that "PRO326 enhances or induces an immune response" credible.

(1) Appellants have discussed throughout prosecution that PRO326 is not an irritant but is a proinflammatory molecule, and further, that PRO326 does not cause a hypersensitive reaction. (See, for example, Appeal brief filed October 3, 2005 and amended Appeal brief of May 15, 2006). Applicants added that by definition, hypersensitive reactions need prior exposure to the antigen (or irritant) in question, in order to elicit an immune response. In this instance, the animal (guinea pig) in the SVP assay was not pre-exposed or sensitized to PRO326. Therefore, one skilled in the art would find the Appellants conclusion that "PRO326 is an inflammatory molecule due to the positive reaction in the SVP assay" scientifically sound and logical.

Yet, the Examiner continues to maintain that PRO326 is an "irritant," and asserts that the reasoning for her conclusion(s) is/are scientifically sound (page 11, lines 23-24). The Examiner adds that "lye and acid were cited as extreme examples of compositions that would cause the same result observed for PRO326," without providing any evidentiary support from the art for the Examiner's position (page 10, lines 17-18).

Appellants strongly disagree. The Examiner seems to miss the point that only certain human secretory molecules disclosed in the specification were shown to mount an inflammatory response, or tested positive in the SVP assay (see Example 77, last line), whereas, many other PRO molecules that were also studied simultaneously, did not show such an inflammatory response in this SVP assay (negative controls). Therefore, not every human polypeptide, (or for that matter, lye or acid) injected into the guinea, or measured in this assay, would be expected to give a positive result. Therefore, most of the Examiner's arguments asserting that PRO326 is an irritant is completely incorrect. Further, the Examiner's reasoning is not scientifically sound because, as mentioned before, the animal (guinea pig) in the SVP assay was not pre-exposed or sensitized to PRO326. Appellants submit that the Examiner's rejections are based on several misconceptions of the field of inflammation and erroneous conclusions thereof. On the other hand, one skilled in the art would clearly understand and correctly interpret the results of this assay.

Additionally, the Utility standard (cited above) clearly states that the Examiner **has the initial burden to offer evidence** to show that one of ordinary skill in the art would have a

legitimate basis for doubting the credibility of the data in Example 77 and for asserting utility based on their data. Instead, the Examiner **has not cited any reference(s)** from the art in support of his/her position that (1) results of the SVP assay would make the skilled artisan conclude that the molecule is an irritant, or (2) "basic irritants, such as lye, would test positive in the Miles assay."

To that, the Examiner asserts that the "Appellants repeatedly argue that the Examiner has failed to cite evidence to support the finding of lack of utility. Specific evidence that PRO326 polypeptide is not a proinflammatory molecule **is neither required nor possible, as the Examiner does not possess laboratory facilities**. As set forth in the MPEP, a finding of lack of utility may be properly made if there is a scientific basis to doubt the assertion of utility." (emphasis added; page 11, second paragraph of the Examiner's Answer).

Appellants respectfully disagree. The M.P.E.P. clearly states that, "It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art. *In re Ahlert*, 424 F.2d at 1091, 165 USPQ at 420-21. See also *In re Grose*, 592 F.2d 1161, 1167-68, 201 USPQ 57, 63 (CCPA 1979), M.P.E.P. 2144.03. Besides, Appellants submit that, it seems that the Examiner is relying on his/her own "common knowledge" in making this rejection. However, such a rejection would not be sufficient to meet the requirements for a *prima facie* case for a utility rejection, for the reasons discussed below. In fact, it is also asserted by the Federal Circuit that, "[i]t is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based." *In re Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697 (Fed. Cir. 2001). Therefore, the Examiner has clearly **not met** the initial burden of offering evidence to show that one of ordinary skill in the art would have a legitimate basis for doubting the credibility of the conclusions drawn from the positive result in Example 77 and for asserting utility thereof. The Examiner seems to rely on his/her own "common knowledge" in making this rejection, which as discussed above is inappropriate.

Yet, even without the Examiner having met this initial burden of offering countervailing evidence, Applicants have provided rebuttal evidence to the arguments. For instance, Appellants

provided the Rampart *et al.* (*Am J Pathol* **135(1)**:21-25 (1989)) reference (submitted by Appellants with response of July 22, 2003) that identified IL-8 using a rabbit skin neutrophil accumulation assay similar to the present SVP assay. Rampart *et al.* suggested the involvement of endogenous IL-8 in an acute phase inflammatory response of an animal to a microbial stimulus and further disclosed suggestive data supporting its involvement in psoriasis (see page 24, column 1, last paragraph). Further, the Fong Declaration detailed the state of the art of inflammation and provides art accepted examples of the usefulness for proinflammatory molecules. Therefore, it is more likely than not that those skilled in the art, to a reasonable probability, would believe that the claimed polypeptide is useful because it encodes a proinflammatory molecule, and therefore, is useful for generating antagonistic molecules, like antibodies, against PRO326, to treat diseased conditions involving inflammation.

Therefore, Appellants submit that one skilled in the art would easily conclude that PRO326 is an inflammatory molecule due to the positive reaction in the SVP assay and would acknowledge that this reasoning is scientifically sound and logical.

(2) The Examiner asserts that "it has not been shown that **PRO326 is produced by guinea pigs**". Appellants submit that, as is stated clearly in the specification, secretory polypeptides like PRO326 are **human** secretory proteins (see field of invention, introduction, of the instant specification). Therefore, PRO326 is not expected to be produced by the guinea pig. Even assuming arguendo, if there supposedly were regions of homology between the human PRO326 molecule and any guinea pig protein, which Appellants strongly do not concede to, such homologous regions, being self-antigens for the guinea pig, would not be expected to mount an immune/ inflammatory response to PRO326. Therefore, any rejection based on the notion that "PRO326 (maybe) produced by guinea pigs" is nonsensical and should not be applied in this instance. Appellants submit that the Examiner's conclusions that PRO326 is an "irritant" or causes "a hypersensitive reaction" has no logical basis, and stems from misconceptions regarding the field of inflammation. For these reasons alone, one skilled in the art would never conclude that PRO326 is an irritant or a self-antigen.

(3) The Examiner also inquires "**what types of cells may have migrated to the**

wound response."

Example 77 (page 210) which describes a dye-based proinflammatory cell infiltration assay clearly discloses inflammatory polypeptides as **"inducing mononuclear cell, eosinophil and PMN infiltration at the site of injection of the animal" (page 210, lines 23-24 of the specification)**. Further, the types of cells migrating to the site of injection in response to inflammation were also well known in the art at the time of filing, as detailed in the Fong Declaration and demonstrated in the Exhibit B: "Regulation of Leukocyte movement" attached therein.

The Examiner adds that the SVP results are preliminary and asserts that "substantial further experimentation would be required to determine a utility for PRO326."

Appellants respectfully disagree and submit that "(t)he mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility." M.P.E.P. §2107.01 III cites *In re* Brana, 51 F.3d 1560, 34 U.S.P.Q. 2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law....necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is readily to be administered to humans." Further, "to violate §101, the claimed device must be totally incapable of achieving a useful result." *Juicy whip Inc. v. Orange Bang Inc., 51* U.S.P.Q. 2d 1700 (Fed. Cir. 1999), *citing Brooktree corp. v. Advanced Micro devices, Inc.,* 977 F.2d 1555, 1571 (Fed. Cir. 1992). Therefore, the Examiner's interpretation that, patentability precludes any further experimentation is incorrect.

On pages 23-24, last few lines, the Examiner asserts that "with respect to the use of anti-PRO326 as an anti-inflammatory compound, one would first have to show that PRO326 is *produced* as part of an inflammatory response *in vivo* for such to constitute a substantial assertion. that has not been done." (emphasis in original).

Appellants respectfully disagree. For the reasons discussed under point (2), Appellants submit that PRO326 polypeptides are **human** secretory proteins (see field of invention, introduction, of the instant specification) and are not expected to be produced by the guinea pig. The Examiner seems to interpret this SVP data form her own utility standards. According to the Utility guidelines provided by the USPTO, no such showing need be made for asserting substantial utility. The Examiner seems to miss the point that the guinea pig is the experimental tool, which

mounts an inflammatory response to PRO326 in this assay. Only some secretory molecules disclosed in the specification mounted such an inflammatory response or tested positive (see Example 77, last line), whereas many other PRO molecules, that were also studied simultaneously, did not show such a response (negative controls). Therefore, not every human polypeptide, (or for that matter, lye or acid) injected in this assay would be expected to give a positive result in the SVP assay. Therefore, most of the Examiner's arguments asserting that PRO326 is an irritant is nonsensical, because then, likewise, other PRO molecules tested in this assay would also have given a positive, irritant or hypersensitive reaction, which did not occur. Appellants once again

Further, as asserted before, the SVP assay is an *in vitro* assay for identifying potential inflammatory molecules. In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a Examiner decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

The *Fujikawa* case was in the context of utility for pharmaceutical compounds and the principals stated by the Court are applicable in the instant case. Utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility. In this instance, there is "sufficient correlation" between a positive result in the SVP assay (*i.e.*, a proinflammatory molecule) and utility in disease conditions like cancer and autoimmune disease.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds.

Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, *i.e.,* there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (Emphasis added).

The *Cross* case is very similar to the present case. Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Appellant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Accordingly, in view of the disclosure of the present application, one of ordinary skill in the art would understand how to make and use the claimed PRO326 polypeptides without undue experimentation and would not find the disclosure preliminary.

Therefore, Appellants submit that the present application discloses the utility of the subject matter of the instant claims and that one of skill in the art would know exactly how to use the claimed PRO326 polypeptides, for instance, to make polypeptides effective for inducing inflammation and for preparing antibodies to reduce inflammation, without any undue experimentation. The specification provides detailed guidance as to how to identify and make nucleic acids encoding polypeptides having complete amino acid sequence identity to PRO326 polypeptides. The specification also provides ample guidance to allow the skilled artisan to identify those polypeptides which meet the limitations of the claims, found in Example 77 (page 210, lines 22) which describes a dye-based proinflammatory cell infiltration assay in which PRO326 polypeptides induce inflammation, or as "inducing mononuclear cell, eosinophil and

PMN infiltration at the site of injection of the animal" (page 210, lines 23-24 of the specification). Accordingly, in view of the disclosure of the present application, one of ordinary skill in the art would understand how to make and use the claimed PRO326 polypeptides without undue experimentation. Thus, this rejection of Claims 39-41 and 43 should be withdrawn.

II. *Claim Rejection Under 35 U.S.C. §102*

Claims 39-41 and 43 remain rejected under 35 U.S.C. §102(e) as allegedly anticipated by Wu *et al.*, U.S. Patent No. 6,046,030 (filing date of December 8, 1997), and as allegedly anticipated by Wang *et al.*, U.S. Patent No. 6,426,072 (filing date of August 21, 2000). Appellants submit that the antibodies of Claims 39-41 and 43 are not anticipated by the cited references.

Anticipation under 35 U.S.C. §102 requires that every element of the claimed invention be identically shown in a single reference.[1] Moreover, [t]hat which would *literally* infringe if later in time anticipates if earlier than the date of invention.[2] Conversely, it follows that which would *not* infringe if later does not anticipate if earlier.

The rejection over U.S. Patent No. 6,045,030

The Examiner presents Wu as discussing a polypeptide (SEQ ID NO:5) **with 50 % identity to residues 1-1083 of SEQ ID NO:294.** Appellants note that SEQ ID NO:294 includes 1119 amino acid residues. Thus, the recited sequence identity is not calculated with respect to the full-length sequence, as is usually done. If it were calculated in that way, the sequence identity would presumably be even less than 50%. Appellants note that the claimed antibodies are antibodies that specifically bind to SEQ ID NO:294; antibodies that fail to bind specifically to SEQ ID NO:294 do not fall within the claims, and fail to anticipate the present invention. Appellants respectfully submit that the terms "specific binding" and "specifically binds" are well known

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[1] *In re Bond*, 910 F.2d 831,832, 15 U.S.P.Q.2d 1566,1567 (Fed. Cir. 1990).

[2] *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987), *cert denied*, 484 U.S. 1007 (1988).

terms of art in antibody technology. One skilled in the art understands that "specifically binds" means that an antibody binds to a unique epitope within a target sequence. Example 16 of the U.S. Patent Office's Synopsis of Application of Written Description Guidelines clearly acknowledges that considering the routine and art-recognized methods of making antibodies, the well defined characteristics of the five classes of antibodies, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, the disclosure of an antigen implicitly discloses an antibody which binds to that antigen. This general determination is equally true to antibodies which "specifically bind" to a target antigen, since such antibodies can be identified by routine screening in routine competitive binding assays.

Applicants respectfully point out that methods of determining antibody binding specificities are well known in the art, and disclosed in the instant specification. It is understood that because non-specific cross reactions have different and lower binding affinities than the specific binding reaction, a competitive binding assay can distinguish these cross reactions from the specific reaction. One of skill in the art would therefore understand that an antibody that specifically binds to SEQ ID NO:294 is one which does not significantly cross react with other antigens, as tested in competitive binding assays between SEQ ID NO:294 and the other antigens.

The specification provides methods to determine whether an antibody specifically binds to epitopes possessed by SEQ ID NO:294. Routine methods of determining antibody binding specificities, including immunoprecipitation, or competitive binding assays such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA), are disclosed in the specification at, for example, page 391, lines 6-9. Methods of determining the binding affinities of antibodies using Scatchard analysis are disclosed at page 391, lines 9-10.

Applicants further note that patents routinely issue with claims to antibodies that "specifically bind" to target polypeptides. See, for example, the claims of U.S. Patent No. 6,596,498 (Bone Stimulating Factor, issued July 22, 2003); and U.S. Patent No. 6,852,839 (Fhm, a Novel Member of the TNF Ligand Supergene Family, issued February 8, 2005); U.S. Patent No. 6,884,594 (Antibodies to Growth Factor HTTER36, issued April 26, 2005); U.S. Patent No. 6,884,879 (AntiVEGF Antibodies, issued April 26, 2005);and U.S. Patent No. 6,911,531

(Antibodies Directed Towards a Novel Human EP Prostaglandin Receptor, issued June 28, 2005). The specifications of these patents do not include explicit definitions of antibodies that "specifically bind." The fact that these patents issued demonstrates that the term "specifically binds" has a well understood meaning in the art of antibody technology.

Appellants note that the claimed antibody or antibody fragment specifically binds to the polypeptide of SEQ ID NO: 294. Non-specific binding is not within the terms of the claim. Appellants submit that an antibody directed at a polypeptide with a stated of sequence identity of merely 50% to the target polypeptide of SEQ ID NO: 294 is not one that specifically binds to the polypeptide of SEQ ID NO: 294. Thus, antibodies directed to the Wu sequence are not encompassed by the instant claim, and therefore, this reference does not anticipate the claimed invention.

For at least the above reasons, one skilled in the art would understand what is meant by the phrase "specifically binds," and would understand exactly what is comprised within the scope of the claims. Appellants respectfully submit that this rejection is overcome.

The rejection over U.S. Patent No. 6,426,072

As discussed above, support for the present claims is found in the parent international application PCT/US98/19437, filed September 17, 1998, in addition to that disclosed in the present application. Thus, Appellants are entitled to an effective filing date of 17 September, 1998. Being filed after the effective filing date of the present application, Wang is not prior art under 102(e).

Accordingly, Appellants respectfully submit that the claim rejections under 35 U.S.C. § 102(e) are overcome.

III. *Claim Rejections* Under 35 U.S.C. §103(a)

Claims 39-41 and 43 remain rejected as allegedly obvious over Kawai *et al.* (priority date of June 1, 2001) or Nagase *et al.* (priority date of May 1, 1999) or Suzuki *et al.* (priority date of February 1, 1997) any of the three in view of Sibson *et al.* (WO 94/01548; publication date 1/20/94) under 35 U.S.C. §103(a). The Examiner alleges that Sibson outlines generally that it is

useful to place a desired cDNA sequence into an expression vector, host cell and to raise antibodies to the protein encoded by the cDNA. Thus, the Examiner alleges that it would be obvious to a person of ordinary skill in the art to make antibodies to any of the proteins disclosed by Kawai, Nagase or Suzuki according to the teachings of Sibson. Appellants submit that the present invention is not obvious over any combination of the cited references.

As discussed above, Applicants are entitled to at least an effective filing date of 17 September, 1998. For this reason at least Nagase and Kawai are not prior art.

Suzuki discusses a polypeptide that has 50.14% identity to the amino acid residues of SEQ ID NO:294. As discussed above, by the terms of the claims, only those antibodies that specifically bind to the polypeptide of SEQ ID NO:294 fall within the claims. Thus, since an antibody directed to the Suzuki sequence is not one that would specifically bind to the polypeptide of SEQ ID NO:294, such an antibody is not within the instant claims, and would not anticipate the present invention. Therefore, the Suzuki reference not providing antibodies of the claimed invention, it fails as anticipatory prior art.

Since Kawai, Suzuki and Nagase fall as primary references, failing to provide antibodies within the present claims that might have been disclosed prior to the present invention, and since the teachings of Sibson do not teach or make obvious the sequence of SEQ ID NO:294, any combination of some or even of all the cited references fails to provide all the elements of the claimed invention and so fails to make the present claims obvious.

Accordingly, Appellants respectfully submit that the rejections of Claims 39-41 and 43 under 35 U.S.C. §103(a) is overcome.

CONCLUSION

For the reasons given above, Appellants submit that the Skin Vascular Permeability assay disclosed in Example 77 of the specification provides at least one asserted specific and substantial patentable utility for the PRO326 polypeptides claimed in Claims 39-41 and 43, and that one of ordinary skill in the art would accept this asserted utility as credible and would understand how to make and use the claimed polypeptides. Therefore, Claims 39-41 and 43 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. Accordingly, reversal of all the rejections of Claims 39-41 and 43 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618 P2C28**.

Respectfully submitted,

Date: October 2, 2006

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